

REMARKS

The present invention relates in part to assay methods for specifically detecting and/or quantifying bcr-abl gene rearrangements. In particular, the presently claimed methods can provide highly reproducible qualitative and quantitative results in which the presence and/or amount of three different bcr-abl translocations may be determined in a single assay.

Claims 1-12 are presently pending in the instant application. Applicants have amended claim 1 herein. These amendments do not introduce new matter or require a new search, and are merely provided to aid the Examiner in understanding the instantly claimed invention, as discussed hereinafter. The amendments to the claims are not made for purposes of patentability, and do not further limit the claims as originally filed.

Notwithstanding the foregoing, Applicants expressly reserve the right to pursue subject matter no longer claimed in the instant application in one or more applications which may claim priority hereto. Applicants respectfully request reconsideration of the claimed invention in view of the foregoing amendments and the following remarks.

Non Art-Related Remarks

35 U.S.C § 112, Second Paragraph

Applicants respectfully traverse the rejection of claims 1-12 under 35 U.S.C. § 112, second paragraph, as allegedly being indefinite for failing to particularly point out and distinctly claim the present invention.

When determining definiteness, the proper standard to be applied is "whether one skilled in the art would understand the bounds of the claim when read in the light of the specification." *Credle v. Bond*, 30 USPQ2d 1911, 1919 (Fed.Cir.1994). See also *Miles Laboratories, Inc. v. Shandon, Inc.*, 27 USPQ2d 1123, 1127 (Fed.Cir.1993) ("If the claims read in the light of the specification reasonably apprise those skilled in the art of the scope of the invention, § 112 demands no more.").

“primers and probes set forth in SEQ ID Nos: 1-8”

Applicants respectfully disagree with the Examiner's assertion that the phrase “primers and probes set forth in SEQ ID Nos: 1-8” in claim 1 is allegedly indefinite [and that] it is unclear if it is intended to be markush language, or if the use of all 8 nucleic acids in the method are required.” Paper No. 10, page 2. Applicants respectfully submit that one skilled in the art would reasonably understand that the phrase refers to use all 8 nucleic acid in the invention assay method in light of the specification. Nevertheless, in an effort to advance prosecution, Applicants have amended claim 1 to explicitly recite that each of the primers and probes set forth in SEQ ID Nos: 1-8 are used. Applicants respectfully submit that the foregoing amendments render the rejection moot.

“Real Time PCR”

Applicants respectfully disagree with the Examiner's assertion that the phrase “real time PCR” in claims 2 and 3 is allegedly indefinite as “all PCR amplification reactions are conducted in real, as opposed to imaginary time.” It is respectfully submitted that the Examiner's interpretation of the phrase fails to consider the reasonable understanding of this phrase within the relevant art. *See, e.g.*, MPEP §2173.02 (“Definiteness of claim language must be analyzed, not in a vacuum, but in light of... [t]he teachings of the prior art; and [t]he claim interpretation that would be given by one possessing the ordinary level of skill in the pertinent art at the time the invention was made”).

The term “real time PCR” is well known to those of skill in the art as referring to specific PCR methods in which a signal emitted from the assay is monitored during the reaction as an indicator of amplicon production during each PCR amplification cycle (*i.e.*, in “real time”), as opposed to conventional PCR methods, in which an assay signal is detected at the endpoint of the PCR reaction. As an indication of the acceptance of this term by those of skill in the art, Applicants note that a search of the *Medline* database reveals 383 publications in which the term is used in the title. *See, e.g.*, Appendix B (providing the first page of this search). Indeed, the Eder

et al. and Mensink et al. publications cited by the Examiner in Paper No. 10 each use this phrase both in their titles and throughout the bodies of the publications.

Applicants respectfully submit that, because of its common usage by those of ordinary skill in the art, the skilled artisan is reasonably apprised of the scope of the present claims with regard to the phrase "real time PCR." 35 U.S.C. §112, second paragraph, demands no more. Therefore, because the claims, when properly interpreted, meet the standards of 35 U.S.C. §112, second paragraph, Applicants respectfully request that the rejection be reconsidered and withdrawn.

Art-Related Remarks

35 U.S.C. § 103

Applicants respectfully traverse the rejection of claims 1-6 and 8-12 under 35 U.S.C. § 103(a) as allegedly being unpatentable over Mensink *et al.* (British J. Haematol. (August 1998): 102: 768-774) in view of Hariharan *et al.* (EMBO J. 6(1): 115-119, 1978) and further in view of Shtivelman (Cell 47: 277-284, 1986).

To establish a *prima facie* case of obviousness, three criteria must be met: there must be some motivation or suggestion, either in the cited references or in knowledge available to the ordinarily skilled artisan, to modify or combine the references; there must be a reasonable expectation of success in combining the references; and the references must teach or suggest all of the claim limitations. *In re Vaeck*, 20 USPQ2d 1438 (Fed. Cir. 1991) *See also*, MPEP §2143.

As discussed above, the instant invention can provide highly reproducible qualitative and quantitative results in which the presence and/or amount of three different bcr-abl translocations may be determined in a single assay by using the eight specifically designed primers and probes recited in the claims.

In contrast, the Mensink *et al.* publication discloses a method for quantitation of a bcr-abl cDNA fragment using only one set of primers and one probe for bcr-abl fragment. The primers disclosed in the Mensink *et al.* publication are different from those recited in the present claims.

However, the Examiner contends that the Mensink *et al.* publication discloses "primer selection" generally; that the Hariharan and Shtivelman references disclose the cDNA sequences for BCR and ABL coding regions, respectively; and that "the claimed primers simply represent structural homologues, which are derived from sequences suggested by the prior art as useful for primers and probes." Paper No. 10, pages 5-6. This assertion by the Examiner, however, is both incorrect and fails to consider the proper standard by which obviousness must be determined.

Applicants respectfully note that there is nothing, other than the Examiner's bare assertion, to indicate that the primers referred to in the instant claims are "structural homologues" of the primers disclosed in the Mensink *et al.* publication. While it is true that each is a nucleic acid, and that each is a sequence of four basic nucleosides, any homology between the sequences recited in the present claims and those of the cited publications ends there. The Examiner's position that this similarity renders such molecules "homologues" is akin to arguing that a dictionary renders *Moby Dick* obvious because each represents the same words, albeit in a different sequence. Applicants respectfully submit that the Examiner's conclusion of "structural homology" is incorrect, and request that the Examiner indicate a basis for asserting that the claimed set of eight primers and probes are "simply... structural homologues" of those disclosed in the prior art.

Furthermore, to provide a *prima facie* case of obviousness, there must be some motivation, either provided by the cited publications themselves or in the knowledge generally available in the art, to arrive at the specific combination of elements recited in the present claims. *See, In re Dance*, 48 USPQ2d 1635, 1637 (Fed. Cir. 1998) (there must be some motivation, suggestion, or teaching of the desirability of making the specific combination that was made by applicant); *see also, In re Kotzab*, 55 USPQ2d 1313, 1317 (Fed. Cir. 2000) ("particular findings must be made as to the reason the skilled artisan, with no knowledge of the claimed invention, would have selected these components for combination in the manner claimed" in order to support an obviousness rejection) (emphasis added). The Examiner has not indicated why, from amongst the many thousands of possible sequences available for use as primers and probes, the skilled artisan would have arrived at the specific sequences referred to in the instant claims. In

the absence of particular findings in this regard, no *prima facie* case of obviousness has been established.

Moreover, even if the Examiner is correct that a *prima facie* case of obviousness has been established, such a *prima facie* case may be rebutted by evidence of superior results. *See, e.g.*, MPEP §2144.09. As noted above, the instant claims provide methods by which the presence and/or amount of three different bcr-abl translocations may be determined in a single assay. In contrast, of the publications cited by the Examiner, only one (the Mensink *et al.* publication) detects any bcr-abl translocations are detected, and the methods disclosed in that publication can detect only a single translocation. Thus, Applicants respectfully submit that the superior results provided by the presently claimed methods rebut any *prima facie* case of obviousness may have been established by the Examiner.

Therefore, because no *prima facie* case of obviousness has been established, or, in the alternative, any *prima facie* case of obviousness may have been established has been rebutted, Applicants respectfully request that the rejection under 35 U.S.C. §103 be reconsidered and withdrawn.

Likewise, Applicants respectfully traverse the rejection of claims 1-12 under 35 U.S.C. § 103(a) as allegedly being unpatentable over Eder *et al.* (Leukemia (September 1999) 13: 1383-1389) in view of Hariharan *et al.* (EMBO J. 6(1): 115-119, 1978) and further in view of Shtivelman (Cell 47: 277-284, 1986) and further in view of Ercolani *et al.* (Journal of Biological Chemistry (1988) 263(30):15335-15341).

It is respectfully submitted that the primers disclosed in the Eder *et al.* publication, like those discussed above from the Mensink *et al.* publication, are different from those recited in the present claims. Moreover, as in the rejection based on the Mensink *et al.* publication, the Examiner's rejection is predicated upon an allegation that "the claimed primers simply represent structural homologues, which are derived from sequences suggested by the prior art as useful for primers and probes." Paper No. 10, page 10.

Thus, as above, Applicants respectfully submit that the Examiner's conclusion of "structural homology" is incorrect, and request that the Examiner indicate a basis for asserting that the claimed set of eight primers and probes are "simply... structural homologues" of those disclosed in the prior art. Additionally, The Examiner has not indicated why, from amongst the many thousands of possible sequences available for use as primers and probes, the skilled artisan would have arrived at the specific sequences referred to in the instant claims. In the absence of particular findings in this regard, no *prima facie* case of obviousness has been established.

Moreover, as above, even if the Examiner is correct that a *prima facie* case of obviousness has been established, such a *prima facie* case is rebutted by the superior results provided by the presently claimed methods. In this regard, Applicants note that the instant claims provide methods by which the presence and/or amount of three different bcr-abl translocations may be determined in a single assay. In contrast, of the publications cited by the Examiner, only one (the Eder *et al.* publication) detects any bcr-abl translocations are detected, and the methods disclosed in that publication can detect only two translocations.

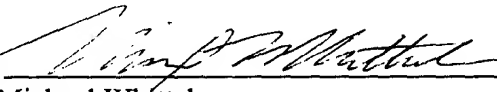
Therefore, because no *prima facie* case of obviousness has been established, or, in the alternative, any *prima facie* case of obviousness may have been established has been rebutted, Applicants respectfully request that the rejection under 35 U.S.C. §103 be reconsidered and withdrawn.

CONCLUSION

In view of the foregoing remarks, Applicants respectfully submit that the pending claims are in condition for allowance. An early notice to that effect is earnestly solicited. Should any matters remain outstanding, the Examiner is encouraged to contact the undersigned at the address and telephone number listed below so that they may be resolved without the need for additional action and response thereto.

Respectfully submitted,

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Appendix A: Marked up version of the claim amendments, showing the changes made.

1. (Amended) A method for determining bcr-abl translocation rearrangements in a biological sample comprising the steps of:

- a) extracting RNA from a biological sample;
- b) quantifying the extracted RNA;
- c) reverse transcribing the RNA to cDNA;
- d) amplifying the cDNA and detecting a cDNA signal by using each of the primers and probes set forth in SEQ. ID NOS. 1-8;
- e) obtaining a standard curve of cDNA signals from serial dilutions of a leukemic cell line, wherein the cDNA is obtained by repeating steps a) – d) with the RNA from leukemic cell line and not the sample; and
- f) extrapolating a measurement of the leukemic cells present in the sample by comparing the signal from step d) with that from step e).